REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the outstanding rejections of the claims.

Applicants have cancelled claims 4 and 15-18 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in a continuation application

Claim 1 has been amended. New claims 19-22 have been added. Accordingly, claims 1-3, 5-14, and 19-22 are pending after entry of this amendment. No new matter has been added by this amendment. Applicants submit that the amended claim is supported throughout the specification as filed, including at page 10, line 4 and lines 8-15. Applicants submit that the new claims are supported throughout the specification as filed, including at page 4, lines 16-22 and Figure 1.

The specification has been amended. The amendment at page 9, lines 30 and 31 is supported by Figure 1. One of skill in the art would recognize that C1 is located at the amino terminus and C2 is located at the carboxy terminus and the error in the specification was an inadvertent typographical error. The other amendments to the specification were made to add the SEQ ID numbers.

The Examiner determined the elected species is free of prior art. Applicants respectfully request the Examiner search the next species to which claims 1-3, 5-14, and 19-21 are readable on:

1) amino acid T for A1;

2) amino acid W for A2;

3) amino acid EGNK for $(A3)_n$;

4) amino acid L for A4; and

5) amino acid T for A5.

Specification

The specification has been amended to reflect the status of any applications claiming priority to the provisional applications. U.S. Patent Application No. 09/380,447, filed September 1, 1999, claims priority to U.S. Patent Application Nos. 60/103,514 filed October 8, 1998 and 60/134,870 filed May 19, 1999.

Applicants respectfully submit that an application may incorporate essential material by reference to a pending U.S. patent application. MPEP § 608.01(q). Accordingly, Applicants respectfully request removal of the objection to the disclosure.

Drawings

Applicants have included with their response new formal drawings. Applicants respectfully request removal of the objection to the drawings.

Priority

The filing date of the provisional application, U.S. Patent No. 60/139017, contained a typographical error. The specification has been amended to correct the error. The filing date in the specification is now consistent with the Oath filing date of June 14, 1999.

Examiner's Utility Rejection Under § 101

The Examiner rejected claims 1-3 and 5-14 as being directed to nonpatentable subject matter and lacking patentable utility under 35 U.S.C. § 101. The Examiner contends that the claimed library reads on naturally occurring peptides and this is non-statutory subject matter. Secondly, the Examiner contends that the claimed library does not have any utility, except to screen for new and useful products and as such, lacks a specific utility. Applicants respectfully traverse the rejection.

As an initial matter, Applicants have amended claim 1 to clarify that the library is an isolated library. Thus, Applicants respectfully request withdrawal of the rejection of claims 1-3, and 5-14 as being directed to non-statutory subject matter.

The Examiner also contends that the subject matter of claims 1-3 and 5-14 lacks utility. The Examiner states that "there can be no specific use for complex mixtures of a composition

comprised of different components that could exhibit all kinds of reactives and all kinds of products." Applicants respectfully disagree.

An asserted utility must both be specific and substantial. MPEP § 2107.01(1). An asserted utility is "specific" if the utility is specific to the subject matter claimed. As described in the USPTO guidelines at page 5, a specific utility can be established if a specific target is identified. A substantial utility is one that has "real world" use. As described in the utility guidelines, screening assays for identifying compounds that have a "substantial utility" define a real world context of use. (Utility guidelines, p. 6). In addition, an invention may also have a well-established utility.

Applicants' claims are directed to an isolated library of structurally constrained peptides, wherein each cyclic peptide comprises an amino acid sequence C1-A1-A2-(A3)-A4-A5-C2 (SEQ ID NO: 1). The peptide library can be screened against biological molecules to identify members of the library that bind to a particular biological molecule. A subset of residues within the peptide is varied to mimic various bioactive peptides having an identified secondary structure, such as a β-turn, which has proven significant in many biological processes. As such, the peptide library of the invention can be used to screen a wide variety of biological molecules to identify peptides that may bind and effect the function of the biological molecules. The peptide library can also be used inter alia, to screen for biologically active molecules including agonists and antagonists.

Applicants submit that they have established at least one utility that is specific and substantial. The invention provides methods and compositions of identifying a peptide capable of binding a specific binding partner as described in the specification at page 11, lines 24-35. The peptides may be useful as agonists or antagonists. The peptides generated according to the methods of the invention can be candidates for therapeutic agents including enzyme inhibitors, ligand antagonists, ligand agonists, toxins and immunogens. See the specification at page 23, lines 12-14.

Applicants have also provided a specific example based on the native sequence of CD4 hairpin residues (residues 38-45) that binds to gp120 of HIV. In addition, two other turn structures were evaluated including the F-G loop of domain 2 of human Fc-epsilon receptor 1 (R1) and GPLT from the EPO agonist peptide EMP1. The results show that the hairpin scaffold yields more structured peptides. See the specification at page 29. The EPO agonist peptide

EMP1 is known to have agonist activity. Thus, Applicants submit they have established at least one specific and substantially utility for screening for agonists and/or antagonists for targets such as gp120, EPO, and IgE Fc receptor I.

In addition, in Examples 5 and 6, Applicants generated a phage display library of structurally constrained peptides. This phage display library was screened for binding to Fc-epsilon-receptor 1 IgG fusion protein. In Example 6, about 12 clones that bound to the target receptor were identified. The clones binding to the receptor may be used as antagonists that would prevent binding of IgE to its Fc receptor. Such an antagonist could be useful to minimize allergic responses. The results in Examples 5 and 6 further demonstrate that Applicants have established at least one utility for the claimed invention.

Based on the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 101 rejection of claims 1-3 and 5-14.

Examiner's Written Description Rejection Under § 112, First Paragraph

The Examiner has rejected claims 1-3 and 5-14 under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description for the claimed library. The Examiner contends that there is no specific use described for the library. The Examiner admits that Example 6 provides written description for the invention. Applicants respectfully traverse this rejection.

As discussed in MPEP 2163.02, the standard for determining whether an application complies with the written description requirements of § 112, first paragraph, is whether the description clearly allows persons of ordinary skill in the art to recognize that the inventor was in possession of the claimed subject matter as of the filing date. Further, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." MPEP 2163.04. A number of factors can be utilized to establish written description including:

a) full or partial structure;

b) physical and/or chemical properties;

c) functional characteristics;

d) known or disclosed correlation between structure and function;

e) methods of making; and

f) combinations of A-E.

The Examiner contends that there is nothing in the disclosure that discloses a specific use of the peptide.

Applicants have described the structure of their library of peptides and provided several examples of the peptides library. See at least Examples 2, 5, and 6. Applicants have identified several specific targets for their library, including the binding pocket behind the Phe43 binding site in HIV gp120. See Example 2, p. 27, lines 17-20. This library has specific utility in designing ligands that extend into the binding pocket of HIV gp120. See Example 2, p. 27, line 19. These ligands have substantial utility in themselves in that they (1) can serve as antagonists (i.e. by occupying the binding pocket they inhibit CD4 binding to gp 120 which is necessary for entry of HIV into cells) and (2) can be fused with antigenic epitopes thereby presenting exposed epitopes for virus-neutralizing antibodies. See Example 2, p. 27, lines 12-20; Kwong et al., 1998 *Nature* 393:648-659, specifically abstract and pp. 648-649. Thus, Applicants have described a specific use for the peptide library.

Secondly, Applicants describe forming a cyclized peptide, including GPLT from EMP1, a known agonist for EPO. This agonist has been previously shown to have biological activity. The peptide in the hairpin scaffold yields a more structured peptide. See Example 2, page 29, lines 1-12.

Applicants have also provided a third target. The target is the Fc receptor 1 for IgE. As described in Example 5, a peptide library of random peptides having the sequence: XCTWX4LTCX. In Example 6, the library was screened for binding to a specific target, IgE Fc receptor I. From the library, 12 clones were identified. The Examiner admits that Example 6 provides written description for the application. Applicants submit that this example, inter alia, is sufficient to provide adequate description for the peptide library as claimed.

Based on the foregoing, Applicants contend that the specification provides an adequate written description for the claimed library. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of claims 1-3 and 5-14.

Examiner's Indefiniteness Rejection Under § 112, Second Paragraph

The Examiner has rejected claims 1-3 and 5-14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

Applicants have clarified claim 1 by deleting the optional protection of C1 at the carboxy group and C2 at the amino terminus. This element of the peptide library has been moved to new claim 19, which is dependent upon claim 1.

The Examiner maintains that the specification fails to provide proper antecedent basis for the claimed elected species in the specification. Applicants, however, contend that the specification provides proper antecedent support for the claimed elected species. In Applicants' response to the Examiner's restriction requirement Applicants elected the following species, to which claims 1-15 are readable thereon:

1) amino acid T for A1;

2) amino acid W for A2;

3) amino acid EGNK for $(A3)_n$;

4) amino acid W for A4; and

5) amino acid T for A5.

The elected species finds support in Example 4. See Specification, p. 32, beginning at line 16. A tryptophan-tryptophan cross-strand pair at A2 and A4 is optimal for hairpin stability (i.e. C-T-X-EGNK-X-T-C where X = W). See Example 4, p. 32, line 22 and Fig. 8b.

Based on the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of claims 1-3 and 5-14.

Examiner's Novelty Rejection Under § 102(e)

The Examiner rejected claims 1-2, 4, 5, 8, and 9 under 35 U.S.C. § 102(e) as being anticipated by Wrighton et al. I (U.S. Patent No. 5,830,851) or Wrighton et al. II (1996 *Science* 273:458-463). Applicants respectfully traverse this rejection.

A person is entitled to a patent unless "the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention hereof by the applicant for patent." 35 U.S.C. § 102(e). Wrighton II is a research article, not a patent granted on an application for patent filed in the United States or on an international application which fulfills the requirements of 35 U.S.C. § 371(c). Consequently, Wrighton II cannot properly be asserted as a basis for a novelty rejection under 35 U.S.C. § 102(e). Applicants have directed their response as it applies to Wrighton II as if claims 1-2, 4, 5, 8, and 9 were rejected under 35 U.S.C. § 102(b).

In order for a reference to anticipate a claim, the reference must disclose each and every element of the claim. Applicants submit that neither of the Wrighton references disclose every element of the claims 1-2, 4, 5, 8 and 9.

The Examiner maintains that the specific library disclosed by Wrighton I fully meets the claimed library of peptides having any of the various definitions for the A1-A5 variables comprised in the peptide sequence. However, the Wrighton et al. references do not disclose at least the element that each cyclized peptide in the library includes a sequence: C1-A1-A2-$(A3)_n$-A4-A5-C2. Applicants' claims require all cyclized peptides in the library to comprise a specific set of amino acids where A1 and A5 must be W, Y, F, H, I, V, or T and A2 and A4 must be W, Y, F, L, M, I, or V. The libraries of Wrighton I and II contains peptides outside of this requirement. For example in Wrighton I, in the positions analogous to A1 and A5 in the Wrighton I library, A1 must be R, H, or L and A5 must be D, E, I, L or V. See Wrighton I, col. 169, lines 1-12 and Fig. 2-1 and 2-2. In Applicants' claimed library A1 cannot be R or L and A5 can never be D or E.

Moreover, in the position analogous to $(A3)_n$ in the Wrighton I library, n must always be 4 and A3 must always begin with G followed by P and end in T (i.e. G-P-X-T where X = any of the 20 genetically coded L-amino acids). See Wrighton I, col. 169, line 8 and Fig. 2-1 and 2-2. In Applicants' claimed library, A3 may be 3-12 amino acids in length and positions 1, 2, and 4 of A3 are not constrained to specific amino acids when n equals 4. See Example 4 where $(A3)_n$ is EGNK when n equals 4. By teaching that G-P-X-T is required, Wrighton I does not teach all the subspecies of Applicants' genus. The library in Wrighton I, therefore, does not meet Applicants' claims because not every peptide in the Wrighton I library is as required by Applicants' claimed library.

The Examiner maintains that the broadly claimed peptide library is anticipated by the peptide of Wrighton II. Similar to Wrighton I, Wrighton II discloses a random phage display peptide library with a minimum consensus sequence of YXCXXGPXTWXCXP where X represents positions allowing occupation by several amino acids. In the position analogous to $(A3)_n$ in the Wrighton II library, n must always be 4 and A3 must always begin with G followed by P and end in T (i.e. G-P-X-T). In Applicants' claimed library, A3 may be 3-12 amino acids in length and positions 1, 2, and 4 of A3 are not constrained to specific amino acids when n equals 4. See Example 4 where $(A3)_n$ is EGNK when n equals 4. By teaching that G-P-X-T is required, Wrighton II does not teach all the subspecies of Applicants' genus. The library in Wrighton II, therefore, does not meet Applicants' claims because not every peptide in the Wrighton II library is as required by the claimed library.

Based on the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) rejection of claims 1-2, 4, 5, 8, and 9.

Examiner's Obviousness Rejection Under § 103(a)

The Examiner rejected claims 1, 2, 4, 5, 8, and 9 under 35 U.S.C. § 103(a) as being obvious over Wrighton I or Wrighton II. The Examiner asserts that the libraries disclosed in either Wrighton I or II render the claimed library prima facie obvious. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, the Examiner must show a) that the references disclose all of the elements of the invention, b) that there would be motivation to combine the references to modify the teaching of the reference to obtain Applicants' claimed invention, and c) a reasonable expectation of success. Applicants submit that the Examiner has not established a *prima facie* case of obviousness at least because the references do not disclose all of the elements of the claimed invention, and there is no motivation provided in the references to modify the teachings of the cited references to obtain Applicants' claimed invention.

Applicants' claimed invention is directed to a library of cyclized peptides, each peptide in the library includes a structure CA1-A2-$(A3)_n$-A4-A5-C. In each cyclized peptide in the library, A1 and A5 are independently amino acids W, Y, F, H, I, V or T and A2 and A4 are independently W, Y, F, L, M, I or V.

Applicants submit that the Wrighton et al. I and II references do not disclose all of the elements of Applicants' claimed invention. As discussed previously, the Wrighton et al. references do not disclose a library where each peptide includes the structure C A1, A2, $(A3)_n$, A4, A5 C as claimed by Applicants. The Wrighton et al. references describe libraries that have many other members that do not have the structure as required by Applicants.

In addition, the Wrighton et al. references indicate in position corresponding to A3 in Applicants' claimed invention requires the sequence GPXT. Whereas, in Applicants' claimed invention, A3 can be any peptide with 3-12 amino acids inclusive. Applicants' claimed invention can accommodate a wide variety of β-turn structures.

The Wrighton et al. references do not teach or suggest that their library can accommodate a variety of peptide structures other than GPXT. Thus, Applicants submit that the Wrighton et al. references do not disclose all of the elements of Applicants' claimed invention.

In addition, the Wrighton et al. references do not provide the motivation to one of skill in the art to modify the teachings of Wrighton et al. As discussed previously, in the positions analogous to A1 and A5, Wrighton I teaches A1 must be R, H or L and A5 must be D E I L or V. In Applicants claimed library, A1 cannot be R or L and A5 cannot be D or E. The Wrighton et al. references do not teach or discuss the amino acids in the positions that provide for increased

stability of the hairpin structures in solution. Thus, there would be no motivation based on the disclosure of the Wrighton et al references to modify the teachings of Wrighton et al references to obtain the claimed invention

Accordingly, based on the forgoing differences it is submitted that the references cited in this objection neither teach nor suggest the presently claimed library. Withdrawal of this rejection is respectfully requested.

Conclusion

Applicants submit the claims are in condition for allowance. Notice of such allowance is earnestly solicited. The Examiner is invited to telephone the undersigned for clarification of any of the amendments and remarks or to otherwise facilitate prosecution of the application.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please replace the paragraph beginning at page 1, line 2, with the following rewritten paragraph:

This application claims priority under 35 U.S.C. 119(e) to the U.S. provisional application Ser. No. 60,139,017, filed June 14, 1999, the disclosure of which is expressly incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 12, line 26, with the following rewritten paragraph:

In one aspect, the invention encompasses a peptide library comprising a collection of structurally constrained peptides. Each peptide member of the library comprises amino acid sequence C1-A1-A2-$(A3)_n$-A4-A5-C2 (SEQ ID NO:1), wherein

A1, A2, A3, A4, and A5 are naturally occurring L-amino acids;

the [carboxy]amino terminus of Cysteine C1 is optionally protected with [carboxy]an amino protecting group;

the [amino]carboxy terminus of Cysteine C2 is optionally protected with [an amino] carboxy protecting group;

A1 and A5 are selected from the group consisting of amino acids W,Y, F, H, I , V and T;

Please replace the paragraph beginning at page 12, line 26, with the following rewritten paragraph:

A 16-mer peptide derived from the protein ubiquitin but with a statistically more common turn sequence (MQIGVKNPDGTITLEV (SEQ ID NO: 41)) did form a highly populated hairpin in water (ca. 80%). but the hairpin did not have the same strand register as in the native protein (Searle *et al.* (1995) *Nat. Struct. Biol.* 2:999-1006). Another group studied a similar peptide in which the turn region was replaced with several sequences

(MQIGVKSXXKTITLKV (SEQ ID NO: 42)), wherein XX = pro-ala or pro-gly; Haque & Gellman (1997) *J. Am. Chem. Soc.* 119:2303-2304). Evidence for the hairpin structure, with native strand register, was observed for turns containing D-amino acids but not for L-amino acid sequences. No population estimates were given in this study.

Please replace the paragraph beginning at page 12, line 33, with the following rewritten paragraph:

Several groups have studied model peptides based originally on a sequence from the protein tendamistat. The peptide YQNPDGSQA (SEQ ID NO: 26) shows NMR evidence of a small population of hairpin in water (Blanco *et al.* (1993) *J. Am. Chem. Soc.* 115:5887-5888; de Alba *et al.* (1995) *Eur. J. Biochem* 233:283-292; Constantine *et al.* (1995) *J. Am. Chem. Soc.* 117:10841-10854; Friedrichs *et al. J. Am. Chem. Soc.* (1995) v 117, pp. 10855-10864). A variant of this peptide with strand residues of higher expected β-propensity (IYSNPDGTWT (SEQ ID NO: 27)) was compared to a second peptide with a different turn sequence (IYSNSDGTWT (SEQ ID NO: 28)). Both peptides were estimated by NMR as 30% hairpin in water (de Alba *et al.* (1996) *Fold. Des.* 1:133-144). Further variation of this peptide, predominantly in the turn sequence, yielded hairpins of various structures and mixed populations. Generally no one conformer population exceeded 50% (de Alba *et al.* (1997) *J. Am. Chem. Soc.* 119:175-183). In a final study, the three N-terminal residues in peptide ITSNSDGTWT (SEQ ID NO: 29)) were replaced with various sequences. Again, mixed conformers were frequently observed and populations of a given hairpin conformer were generally less than 50%: one peptide (YITNSDGTWT (SEQ ID NO: 30)) did form a register-shifted hairpin that was highly populated (80%; de Alba *et al.* (1997) *Protein Sci.* 6:2548-2560). The authors of these studies conclude that conformational preferences of the turn residues dominate cross-strand interactions in determining the stability of hairpins, at least in these short model peptides.

Please replace the paragraph beginning at page 13, line 11, with the following rewritten paragraph:

Analysis of hairpin sequences in crystal structures has allowed the design of a different series of β-hairpin peptides. The target structure was a type I' turn flanked by three-residue

strands. Arg-gly sequences were added to the ends to improve stability. The peptide RGITVNGKTYGR (SEQ ID NO: 31) is partially folded into a hairpin conformation (about 30%) as determined by NMR (Ramirez-Alvarado *et al.* (1996) *Nat. Struct. Biol.* 3:604-612). The importance of strand residues is indicated by replacement of the ile and val, the lys and tyr, or all four residues with alanine. None of the alanine-substituted peptides showed any tendency to form a hairpin. The same authors reported a second series of experiments in which position i+1 of the turn was varied (asn to asp, ala, gly or ser). No peptide was more structured than the original sequence with asn in the turn (Ramirez-Alvarado *et al.* (1997) *J. Mol. Biol.* 273:898-912). A review describing this work stated that adding glu-lys pairs to the termini of the model peptide stabilized the hairpin but did not give further details (Ramirez-Alvarado *et al.* (1999) Bioorg. Med. Chem. 7:93-103).

Please replace the paragraph beginning at page 13, line 23, with the following rewritten paragraph:

Another model peptide series (RYVEVXGOrnKILQ (SEQ ID NO: 32)) has yielded evidence for hairpin formation in water. Residue X as D-pro or L-asn yields characteristic NOEs and alpha-H shifts, but the L-pro peptide is unfolded. No population estimates are given, but D-pro appears to give the more stable hairpin (Stanger & Gellman (1998) *J. Am. Chem. Soc.* 120:4236-4237).

Please replace the paragraph beginning at page 13, line 26, with the following rewritten paragraph:

A designed 16-residue peptide (KKYTVSINGKKITVSI (SEQ ID NO: 33)) based on the met repressor DNA binding region formed a hairpin structure in water with an estimated population at 50% at 303 K. Truncation of one strand showed that the turn was populated without the strand interactions, although to a lesser degree (35%). An analysis of the thermodynamic parameters for hairpin formation showed that folding is enthalpically unfavored and entropically driven, with $\Delta G = 0.08$ kcal/mol at 298 K (Maynard & Searle (1997) *Chem. Commun.* 1297-1298; Griffiths-Jones *et al.* (1998) *Chem. Commun.* 789-790; Maynard *et al.* (1998) *J. Am. Chem. Soc.* 120:1996-2007).

Please replace the paragraph beginning at page 13, line 33, with the following rewritten paragraph:

A final hairpin peptide (GEWTYDDATKTFTVTE (SEQ ID NO: 34)) derived from the B1 domain of protein G (GB1) has some features relevant to the peptides of the invention. Unlike the above described model hairpins, the GB1 hairpin has four threonine residues at hydrogen-bonded sites in the strands, including one thr-thr cross-strand pair. This is generally believed to be an unfavorable pairing. In addition, there are trp-val and tyr-phe pairs at adjacent nonhydrogen-bonded sites that might interact to form a small hydrophobic core. The reported data indicate that the GB1 peptide formed a well-populated hairpin (about 50%) in water. The data are consistent with native strand pairing (Blanco *et al.* (1994) *Nat. Struct. Biol.* 1:584-590). A denaturation study of the GB1 peptide allowed estimation of 80% hairpin at 273 K, and analysis of the data (assuming $\Delta Cp = 0$) yielded $\Delta H = -11.6$ kcal/mol, $\Delta S = -39$ cal/mol K: i.e., folding is enthalpically driven and entropically disfavored (Munoz *et al. Nature* (1998) v 390, pp. 196-199). The relative roles of enthalpy and entropy are reversed compared to the met repressor peptide described above.

Please replace the paragraph beginning at page 14, line 20, with the following rewritten paragraph:

The structure of a hexapeptide (Boc-CL-Aib-AVC-NMe) was determined crystallographically, revealing a type II' turn and β-sheet geometry (Karle *et al. J. Am. Chem. Soc.* (1988) v 110, pp 1958-1963). An octapeptide with the same cysteine spacing (ACSPGHCE (SEQ ID NO: 35)) was studied by NMR, and has a similar structure with a turn centered on pro-gly (Walse *et al.* (1996) *J. Comput.-Aided Mol. Des.* 10:11-22). Peptides of the form Ac-CXPGXC-NHMe (SEQ ID NO: 43) were evaluated by measurement of disulfide exchange equilibria, which indicated turn preferences between peptides of as much as 1 kcal/mol (Milburn *et al.* (1987) *J. Am. Chem. Soc.* 109:4486-4496).

Please replace the paragraph beginning at page 14, line 27, with the following rewritten paragraph:

An eleven-residue cyclic peptide (CGVSRQGKPYC (SEQ ID NO: 36)) based on the gene 5 protein from M13 is stably structured in aqueous solution, as demonstrated by NMR

analysis. The cyclic peptide adopts a structure that is quite similar to the corresponding protein loop. The authors claim that well-defined β-hairpin structure had not been previously reported for any unprotected disulfide-constructed cycle (Rietman *et al.* (1996) *Eur. J. Biochem* 238:706-713). This peptide has a val-pro pair at the nonhydrogen bonded sites nearest to the cysteines.

Please replace the paragraph beginning at page 14, line 32, with the following rewritten paragraph:

Cyclization of peptides corresponding to loops from Linulus anti-lipopolysaccharide factor (LALF) based on X-ray structure yielded potent lipid A binders. There is no evidence for structure in these peptides. Several of the peptides have aromatic-aromatic pairs at the nonhydrogen-bonded sites nearest the cysteines; however, the most potent (GCKPTFRRLKWKYKCG (SEQ ID NO:37)) has a pro-tyr pair (Ried *et al.* (1996) *J. Am. Chem. Soc.* 271:28120-28127).

Please replace the paragraph beginning at page 15, line 1, with the following rewritten paragraph:

Disulfide-cyclized peptides from the hairpin region of a rabbit defensin have antibacterial activity exceeding (about 5 to 10-fold) that of the linear analogs. Circular dichroism spectroscopy indicates some non-random structure in phosphate buffer. The more potent peptide (CAGFMRIRGRIHPLCMRR (SEQ ID NO: 38)) has a gly-pro pair at the nonhydrogen bonded sites nearest to the cysteines (Thennarasu & Nagaraj (1999) *Biochem. Biophys. Res. Commun.* 254:281-283).

Please replace the paragraph beginning at page 15, line 6, with the following rewritten paragraph:

A final study describes several peptides from the loops of domain 1 of human CD4. In addition to a disulfide constraint, the authors have added exocyclic aromatic amino acids to the peptide termini. For example, a peptide covering CD4 residues 39-44 was constrained as FCNQGSFLCY (SEQ ID NO: 39). No evidence for structure is given, but one cyclic peptide (FCYICEVEDQCY (SEQ ID NO: 40)) was reported to antagonize both normal CD4 interactions

and those involved in CD4-mediated cell entry by HIV (Zhang *et al.* (1996) *Nature Biotechnology* 14:472-475; Zhang *et al.* (1997) *Nature Biotechnology* 15:150-154).

Please replace the paragraph beginning at page 35, line 4, with the following rewritten paragraph:

Libraries of random peptides fused to the gene 8 protein of the filamentous bacteriophage M13 were produced by Kunkel mutagenesis of plasmid pS1302b, a derivative of pS349 (U.S. patent application No. 09/380,447 which claims priority to U.S. Patent Application Nos. 60/103,514 filed October 8, 1998 and 60/134,870 filed May 19, 1999, incorporated herein by reference). Plasmid pS1302b includes the tac promoter and malE leader sequence of pS349. The hGH sequence and Gly/Ser-rich linker sequence of pS349 were replaced by the sequence:

5'-TAA-TAA-TAA-ATG-GCT-GAT-CCG-AAC-CGT-TTC-CGC-GGT-AAA-GAT-CTG-GGT-GGC-GGT-ACT-CCA-AAC-GAC-CCG-CCA-ACC-ACT-CCA-CCA-ACT-GAT-AGC-CCA-GGC-GGT-3' (SEQ ID NO: 24)

Please replace the paragraph beginning at page 35, line 17, with the following rewritten paragraph:

The form of random peptides was therefore XCTWX$_4$LTCX. A library of 10^9 to 10^{10} individual transformants was prepared by previously described methods (U.S. patent application No. 09/380,447). Approximately one-third of individual clones encoded a functional peptide sequence. The remainder were starting template, contained stop codons, or contained single nucleotide deletions. The library size is thus adequate to include several copies of each possible random sequence.

In the Claims

Please add claims 19-22 and amend the claims to read as shown below.

1. (Amended) [A]An isolated library of structurally-constrained cyclic peptides [comprising a plurality of cyclic peptides], wherein each said cyclic peptide comprises an amino acid sequence C1-A1-A2-$(A3)_n$-A4-A5-C2 [SEQ ID NO:1], wherein

C1 and C2 are cysteines;

A1, A2, A3, A4, and A5 are naturally occurring L-amino acids;

[the carboxy terminus of C1 is optionally protected with a carboxy protecting group;]

[the amino terminus of C2 is optionally protected with an amino protecting group;]

A1 and A5 are independently amino acids W, Y, F, H, I, V, or T;

A2 and A4 are independently amino acids W, Y, F, L, M, I, or V;

A3 is any naturally occurring L-amino acid and n is an integer that is 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; and

C1 and C2 together form a disulfide bond thereby forming a cyclic peptide.

19. (New) The isolated library of claim 1, wherein the amino terminus of Cysteine C1 is optionally protected with an amino protecting group and the carboxy terminus of Cysteine C2 is optionally protected with an carboxy protecting group.

20. (New) An isolated plurality of cyclic peptides having a reverse turn secondary structure, wherein each cyclic peptide comprises the amino acid sequence C1-A1-A2-$(A3)_n$-A4-A5-C2 [SEQ ID NO:1], wherein

C1 and C2 are cysteines;

$(A3)_n$ is a library of natural or synthetic amino acids where n is 3 to 12, inclusive;

A1 and A5 are independently amino acids W, Y, F, H, I, V, or T;

A2 and A4 are independently amino acids W or L; and

C1 and C2 together form a disulfide bond thereby forming a cyclic peptide.

21. (New) The isolated plurality of cyclic peptides of claim 20, wherein the reverse-turn secondary structure is a β-turn, β-hairpin, β-bulge, or γ-turn.

22. (New) The isolated library of claim 19, wherein the amino terminus of Cysteine C1 is protected with an acetate and the carboxy terminus of Cysteine C2 is protected with an amine.